

TOYA129.008APC

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Shirai, et al.	
App. No	: 10/521,958	
Filed	: January 21, 2005	
For	: INDOMETHACIN PREPARATION	EXTERNAL
Examiner	: Jean-Louis, Samira	
Art Unit	: 1617	
Conf No.	: 2101	

2nd DECLARATION OF MAKOTO KANEBAKO AND HITOMI CHIBA
UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

We, Makoto Kanebako and Hitomi Chiba, declare as follows

1. We are researchers in KOWA Company Fuji Research Laboratory. We are familiar with the Office Actions, cited references and claims of the above-referenced application.
2. In order to establish the criticality of a melting point temperature of 40°C or higher, the following experiments were performed. Gel-cream formulations were prepared as described in U.S. Application No. 10/521,958 for Example Formulations 1-3 and Reference Formulations 1-8. See Table 1 (attached).
3. Example Components Glyceryl monostearate, Sorbitan monostearate and Stearyl alcohol having a melting point of 40°C or higher were compared to analogs having a melting point of less than 40°C. The Example and Reference Components are shown in Table 2 (attached).

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4. Example 1 and References 1 and 2 relate to glycerin fatty acid ester. As shown in Table 2, Glycerol monostearate has a melting point higher than 40°C, but Reference Components 1 and 2, Glycerol undecylenate and Glycerol isostearate have melting points under 40°C. In the case of Glycerol undecylenate, the melting point is 36°C, just under 40°C. Referring to Table 1, there is no phase separation for Glycerol monostearate even at one month, whereas phase separation in the two Reference Components is observed at 2 weeks. We conclude that within the genera of glycerol fatty acid esters, only species having a melting point of 40°C or higher (such as Glycerol monostearate) can be stored without phase separation in a gel-cream formulation.

5. Example 2 and References 3, 4, and 5 relate to Sorbitan fatty acid ester. As shown in Table 2, Sorbitan monostearate has a melting point of 40°C or higher. Sorbitan monostearate was compared to three analogs. Sorbitan monoisostearate and Sorbitan monooleate both have the same number of carbon atoms as Sorbitan monostearate (18) but lower melting points. Sorbitan monolaurate has 12 carbons. As shown by the Data of Table 1, there is no phase separation for Sorbitan monostearate having a melting point of 40°C or higher at one month storage. In contrast, Reference Components 3 and 5 showed phase separation at 2 weeks and Reference Component 4 showed phase separation at one month. We conclude that gel-cream formulations which include Sorbitan fatty acid esters with a melting point of 40°C or higher can be stored without phase separation while analogs having a melting point below 40°C cannot be stored without phase separation.

6. Example 3 and References 6, 7, and 8 relate to fatty alcohol. As shown in Table 2, Stearyl alcohol has a melting point of 40°C or higher. The Reference Components, Octyl alcohol, Decyl alcohol and Lauryl alcohol, all have melting points below 40°C. As shown in Table 1, gel-creams formulated with Stearyl alcohol do not show phase separation at one month while the formulations using the fatty alcohols having lower melting points were not even stable initially. We conclude that fatty alcohols having a melting point of 40°C or higher are effective in gel-cream formulations to prevent separation upon storage whereas fatty alcohols having a melting point below 40°C are not effective.

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7. The stabilizing effect of surfactants having a melting point of 40°C or higher in gel-cream formulations and the criticality of the higher melting point could not have been predicted based upon the disclosures of Kimura (JP 10-182458) and Inagi (US 4309414).

8. We declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States codes and that such willful, false statements may jeopardize the validity of the application or patent issuing therefrom.

Dated: November 18, 2008

By: Makoto Kanabako
MAKOTO KANABAKO

Dated: November 14, 2008

By: Hitomi Chiba
HITOMI CHIBA

Table 2 Detail description of surfactant

	Component	Commercial product	Melting point	Length of carbon chain
Example 1	Glyceryl monostearate	NIKKOL MGS-F20	54~58°C	C18
Reference 1	Glyceryl undecylenate	NIKKOL MGD	36°C	C10, unsaturated fatty acid
Reference 2	Glyceryl isostearate	NIKKOL MGIS	below 25°C	C18, branched fatty acid
Example 2	Sorbitan monostearate	NIKKOL SS-10M	55~59°C	C18
Reference 3	Sorbitan monolaurate	RHEODOL SP-L10	13~14°C	C12
Reference 4	Sorbitan monoisostearate	NIKKOL SI-10RV	below 25°C	C18, branched fatty acid
Reference 5	Sorbitan monooleate	RHEODOL SP-O10V	-10°C	C18, unsaturated fatty acid
Example 3	Stearyl alcohol	NIKKOL Stearyl alcohol	56~58°C	C18
Reference 6	Octyl alcohol	KALCOL089g	-15°C	C8
Reference 7	Decyl alcohol	KALCOL109g	7°C	C10
Reference 8	Lauryl alcohol	KALCOL209g	24~27°C	C12